GE Healthcare Position Paper on NSF
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Executive Summary

- Limited data are currently available on the causality of NSF; however case reports have associated the administration of gadolinium-containing contrast agents in renally compromised patients with the development of NSF.
- To date, GE Healthcare (GEHC) has received approximately 200 reports of NSF after Omniscan™ (gadodiamide) Injection administration, usually associated with exposure at high doses. These have been reported to the FDA and global health authorities in accordance with regulatory requirements.
- The case reports of NSF from a number of countries indicate that several gadolinium-containing contrast agents have been associated with the development of NSF.
- Health authorities are requiring label changes for all gadolinium-containing agents.
- Different numbers of spontaneous reports early in an event's history do not necessarily imply a statistically significant difference in risk.
- Predictions of in vivo stability and toxicity of gadolinium chelates based on an in vitro measure of stability such as thermodynamic stability may be inadequate, inconsistent, and potentially misleading.
- GEHC is committed to ensuring the safety of patients, and to keeping our customers fully informed about using our products in the safest and most effective manner. GEHC recommends that all adverse events should be reported promptly to GEHC and to other appropriate regulatory agencies.

Review of Nephrogenic Systemic Fibrosis (NSF)

Nephrogenic systemic fibrosis (NSF) is a rare, but serious, acquired systemic disease. To date, it has only been reported in patients with renal insufficiency, particularly those with severely impaired renal function with glomerular filtration rate (GFR) < 30, who are on or approaching dialysis. At present, there is no evidence that patients without renal impairment are at risk of developing this disease (1). First described in the US in 2000 (2), identifying a case from 1997, NSF was initially thought to be confined to the skin and was therefore named nephrogenic fibrosing dermopathy (NFD). In some patients, however, there is clinical involvement of other tissues (3) (lung, skeletal muscle, heart diaphragm, esophagus, etc.) and is now more commonly referred to as NSF (4). It can be a painful and debilitating condition that can contribute to a fatal outcome.

Risk factors associated with NSF include renal impairment, hypercoagulability states, thrombotic events, recent vascular surgery, recent transplant failure, or sudden onset kidney disease with severe swelling of the extremities (5). Case studies indicate that NSF patients commonly have undergone a vascular surgical procedure or have experienced a thrombotic episode approximately two weeks before disease onset (6). There appears to be no predilection for any race/ethnic group or geographic location. Also, gender and age do not appear to be risk factors. NSF has been reported in children as young as 8 years old (7) and as well as in the elderly, but the majority of NSF reports are in middle-aged patients (5). There is no evidence that immature kidney function in neonates and infants in itself constitutes an increased risk of developing NSF. The reduced level of renal function is physiological in infants and neonates, and therefore normal for age, whereas the reduced renal function in adults in the setting of renal insufficiency is pathological.

While the precise cause of NSF is still under investigation, exposure to gadolinium-based (Gd) magnetic resonance (MR) contrast media (CM), has been reported to be associated with NSF. Cases of NSF have been reported with all Gd-based CM approved for use in the US, indicating that, to the extent there is an association, this may be a class-wide issue, and the FDA has consistently treated it as such (8).

It is difficult to calculate a reliable estimate of an incidence rate or to make determinations regarding the relative safety of Gd-based CM because many of the reported cases of NSF have occurred in clusters and have been based on spontaneous post-marketing reports. However, Deo et al (9) have estimated an incidence rate of NSF in renally impaired patients exposed to Gd to be 4.3 cases per 1000 patient-years. The vast majority of renally impaired patients who receive Gd have not developed NSF.

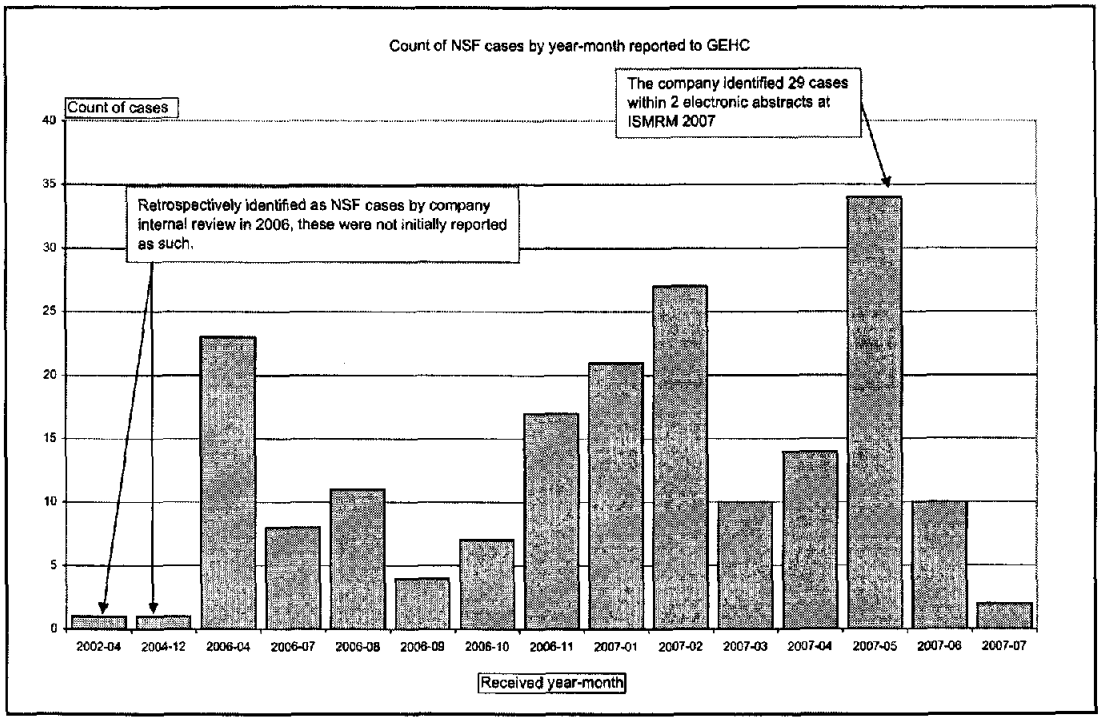
The published literature indicates that other factors, or co-factors to Gd-based contrast agents, are likely involved in the pathogenesis of NSF, and no definite causal link has been established for any Gd-based contrast agent to date (10). Nevertheless, there is a statistical association between Gd-based contrast agents and NSF, which must be addressed in the interest of patient safety. Because of the uncertainty surrounding the cause(s) of NSF, and the possible causal role of Gd-based contrast agents in the development of NSF in renally compromised patients, it is reasonable to assume, until proven otherwise, that Gd-based contrast agents may pose a risk of NSF in patients with renal impairment. However, it also is important to distinguish between an association, which may be coincidental, and actual causation, which is still unknown.

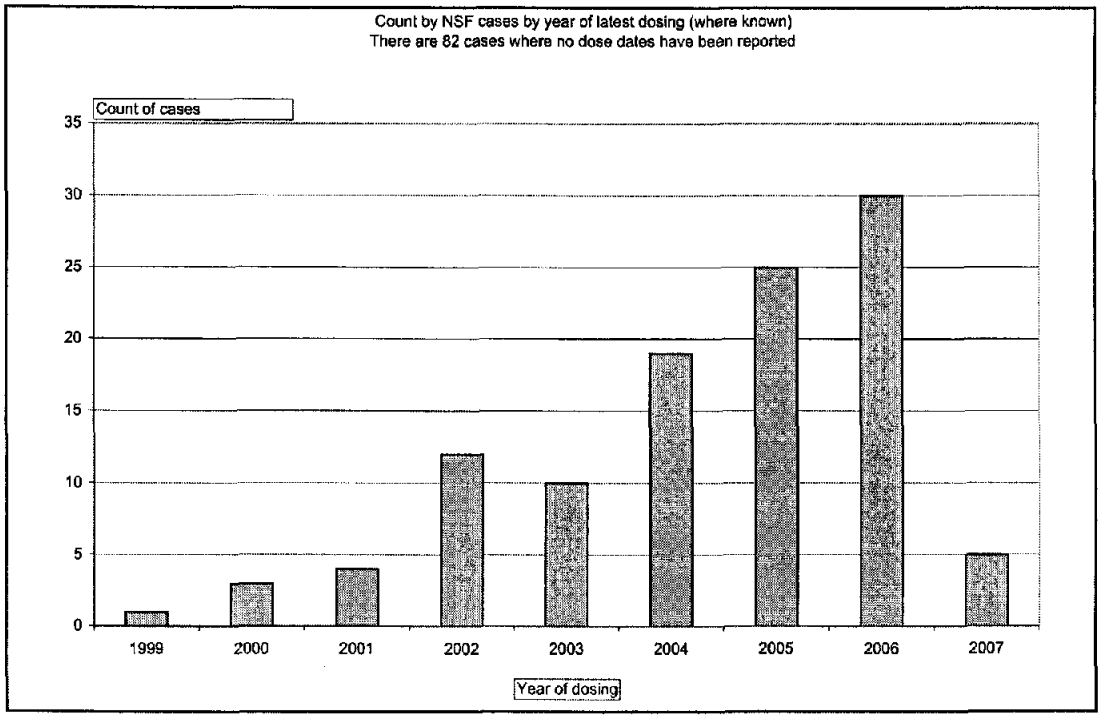
Reports of Contrast Media Involvement in NSF

In April 2006, GEHC promptly reported to health authorities 25 NSF cases that had occurred during a 4-year period at two European hospitals, shortly after GEHC became of aware these case reports and their alleged association to Omniscan. In response to these reports, and in close collaboration with GEHC, the Danish Medicines Agency posted a healthcare advisory on its website 29 May 2006, and the Food and Drug Administration (FDA) published a Public Health Advisory (PHA) on its website on 08 June 2006, alerting the public to these reported cases of NSF (11).

During the same period of time, in June 2006, and in coordination with regulatory authorities, GE Healthcare distributed "Dear Healthcare Professional" (DHP) communications in several European and Asian countries and in the United States, informing healthcare providers about these reported cases of NSF associated with the use of gadodiamide. In December 2006, GEHC sent an updated DHP letter in the US reporting additional cases of NSF. GEHC actively solicited the reporting of any known or suspected cases of NSF associated with the use of Omniscan. Letters were also sent in many European countries in February 2007 in conjunction with a product licence change for all gadolinium agents (described below).

To date, the database of NSF cases reported to GEHC includes approximately 200 cases; these have been reported by GEHC to regulatory authorities worldwide. Most cases originate from the US, and while only recently reported to GEHC, have occurred over a period of several years (see charts below).





Response of Health Authorities

Regulatory agencies have taken a gradual approach, based on a review of the available scientific information, in dealing with the association between Gd-based contrast agents and NSF.

The FDA issued Public Health Advisories (PHAs) applicable to all Gd-based CM in June and December 2006 (11). In May, 2007, the FDA requested label changes for the entire class of Gd-based CM that included a boxed warning (12):

> Gadolinium-based contrast agents increase the risk for nephrogenic systemic fibrosis (NSF) in patients with:
>
> • Acute or chronic severe renal insufficiency (glomerular filtration rate < 30mL/min/1.73m2),
>
> or
>
> • Acute renal insufficiency of any severity due to the hepato-renal syndrome or in the perioperative liver transplantation period.
>
> In these patients, avoid use of gadolinium-based contrast agents unless the diagnostic information is essential and not available with non-contrast enhanced magnetic resonance imaging (MRI). NSF may result in fatal or debilitating systemic fibrosis affecting the skin, muscle and internal organs. Screen all patients for renal dysfunction by obtaining a history and/or laboratory tests. When administering a gadolinium-based contrast agent, do not exceed the recommended dose and allow a sufficient period of time for elimination of the agent from the body prior to any re-administration.

In addition to requesting label changes, the FDA revised information from the December PHA by specifying the patient groups thought to be at risk: the available data show NSF risk in patients with severe renal insufficiency, whether acute or chronic, but not moderate renal insufficiency.

European regulators recommend caution with the use of all gadolinium contrast agents in certain groups of patients, but at this time they have not recommended the same label change for all products. In

February, 2007, in cooperation with the European Community Pharmacovigilance Working Party (PhVWP), GEHC modified its prescribing information to include a contraindication of Omniscan in patients with severe renal insufficiency and in liver transplant patients. The new label also provides that Omniscan should be used in neonates and infants under one year of age only after careful consideration, and with caution in patients with moderate renal insufficiency. At that time the PhVWP also recommended a warning for all other Gd-based CM. In June, 2007 the PhVWP requested changes to the prescribing information for Magnevist comparable to those already effected for Omniscan. In keeping with the incremental, stepwise approach, a question and answer document from the UK Commission on Human Medicines includes a statement that "This issue will be monitored closely as evidence accumulates, and new advice will be issued when necessary".

Please see attached Prescribing Information.

Professional Societies Guidance

The American College of Radiology (ACR) and the European Society of Urogenital Radiology (ESUR) have produced documents to aid healthcare professionals in managing the risk of NSF associated with gadolinium contrast agents. Because each document is produced at a point in time and in a period in which clinical information is dynamic, there are aspects to each report that may require re-evaluation.

In March 2007 the ACR's Blue Ribbon Panel on MR Safety released online (at ajronline.org) the "ACR Guidance Document for Safe MR Practices: 2007" (13). At the time this was published in AJR (June 2007), it was accompanied by an editorial from Dr. van Moore (14), Chairman of the Board of Chancellors of the ACR, laying out the levels of review necessary for the recommendations of this report to become ACR policy, and making clear that, at present, the report represents the opinion of the Blue Ribbon Panel and not official ACR policy.

This more deliberate approach to guidance is warranted in a period of rapidly changing information. As noted above, the recommendations of the FDA have changed between the December, 2006 and May, 2007 PHAs with respect to patients thought to be at risk for NSF. While the Blue Ribbon Panel document on Safe MR Practices (accepted for publication in December, 2006) recommends against use of Omniscan in patients "with any level of renal disease", in May 2007 the FDA clarified earlier reports and stated that it had not received any NSF reports for patients with moderate renal insufficiency (12). It is expected that the Blue Ribbon panel's guidance will likely be reconsidered and amended as new information comes to light.

The ESUR has most recently issued the "ESUR Guideline: Gadolinium based contrast media and Nephrogenic Systemic Fibrosis" dated July 17, 2007 (15). A key feature of those guidelines is to discriminate between gadolinium based contrast agents and to suggest different levels of caution that must be taken with each (specifically, whether to measure serum creatinine before administration of the contrast agent). The conclusion that there are different risk levels is based on numbers of published adverse events reported to date. The contrast agents for which the ESUR states that a creatinine measure is "mandatory" are those which the PhVWP has thus far (mid-2007) recommended be contra-indicated for severely renally compromised patients. As noted previously, the European regulatory agencies are making decisions in an incremental fashion. Initially, these bodies did not contraindicate Magnevist, but have done so in June, 2007, after a substantial number of NSF cases were publicly reported. This raises the question of whether patient safety is best served by trying to discriminate between agents based on incomplete and changing information. Some of the fundamental challenges in dealing with adverse event reporting are detailed in the next section.

Epidemiological Considerations

Relatively recent spontaneous case reports have formed the basis for theories regarding the relation of NSF to gadolinium contrast agents. Important considerations common to epidemiological science should be borne in mind before drawing certain conclusions from those data. The challenges involved in using spontaneous reporting of adverse events to gauge the risk posed by different products was emphasized by the FDA in their May, 2007 Information for Healthcare Professionals: "The lack of complete information of GBCA (gadolinium based contrast agent) exposure, exposure to multiple GBCAs, along with similarities among all these contrast agents, make it impossible at present to definitively determine whether the extent of risks for developing NSF is shared by all GBCAs or vary for some of them." (12)

Many cases of NSF have occurred in clusters and the numbers of reported cases have changed significantly over the months since reporting began, thus making it difficult to calculate a reliable estimate of an incidence rate or to make determinations regarding the relative safety of Gd-based CM. Careful studies to estimate an incidence rate of NSF in renally impaired patients exposed to Gd-based CM (9) suggest that the vast majority of renally impaired patients who receive Gd-based CM have not developed NSF, making it a difficult phenomenon to study based on spontaneous reporting. Other factors that may affect the number of reported cases include:

- **Differences in case definition and handling by manufacturers.** To date, there has not been an effort to harmonize case definition and reporting standards for NSF across all contrast media manufacturers. For example, GEHC has always taken a broad view of what constitutes NSF and a reportable adverse event, and does not require biopsy confirmation or an exclusive link to Omniscan administration before reporting a case to regulatory authorities. Other manufacturers have used a different standard of evidence before concluding that a case may be related to its product.

  GEHC was the first manufacturer to distribute "Dear Healthcare Professional" communications. GEHC has actively solicited the reporting of any known or suspected cases of NSF associated with the use of Omniscan. Thus, it is possible that the early number of reports for Omniscan may be attributable, at least in part, to the fact that GEHC has proactively communicated on this issue and encouraged healthcare professionals to report NSF cases (see Fig. 1).

- **Possible bias in reporting frequency.** Reports to date have shown that cases of NSF occur in clusters from relatively few healthcare institutions and thus do not appear to be independent events. The increased number of early reports of NSF cases associated with Omniscan may, in part, have been due to reporting bias caused by increased physician awareness of the concern around Omniscan. It is well established that spontaneous reporting data do not provide a robust basis for assessments of relative safety since they are susceptible to inaccuracies, recall, and reporting bias. It is possible that this imbalance in awareness of products is responsible for under-reporting of cases associated with other Gd-based contrast agents.

In addition to needing reliable numbers of reported cases, determining the relative risk for different products would require knowing the number of administrations made to the population at risk. While numbers are easily obtainable for total doses of a product shipped to medical professionals, it is not possible at present to determine the doses delivered to individual patients who are severely renally compromised. The number of doses in the at-risk population would not be a simple function of market share when products are used in different clinical settings (tertiary medical centers versus imaging centers), and when products have different approved indications and/or contraindications (e.g. pre-existing contraindications for use in renally compromised patients that were present for some products in European countries).

An uneven distribution of other factors that may contribute to the development of NSF might influence clustering and confound the interpretation of risk based on spontaneous reporting. Also, the appearance of NSF several years after the introduction of Gd-based agents, and the market introduction of some products after NSF began to be manifest, means that estimates of risk for a particular agent based on a simple metric of "doses delivered" will not be an accurate risk assessment.

Stability of Gadolinium Contrast Agents *In Vivo*

Theoretical Considerations

Grobner (16) and Broome et al (17), among others, have suggested that one mechanism by which gadolinium contrast media might trigger NSF is through release of free gadolinium ions, possibly through transmetalation (a reaction in which an endogenous metal such as zinc is exchanged for the gadolinium in the chelate). Broome stated that, if the free gadolinium postulate was true, then gadolinium chelates with lower stability constants would be more likely to release gadolinium and trigger NSF. Broome referred to gadodiamide as one agent with a lower stability constant compared to other agents. Several other publications (18,19) have addressed the stability of Gd-based contrast agents and of Omniscan in particular.

The role of stability constants (including the important factor of selectivity of the ligand for gadolinium over other endogenous metal ions) in the aetiology of NSF is still under scientific investigation. Much of the research conducted to date is in animals or in vitro, and the relevance of such studies to humans must be judged very carefully. Furthermore, the human studies must be viewed in light of the entire body of knowledge on gadolinium contrast agents for proper interpretation, which, apart from the recently reported association with NSF in renally impaired patients, have shown Gd-based contrast agents in general to have a very high overall safety record (20).

The most often quoted measure of stability is the intrinsic thermodynamic stability constant (K_{therm}), reflecting the affinity of a metal for a ligand, and is expressed in logarithmic terms. This number is measured in vitro under extreme conditions that would be incompatible with life, and is greatly influenced by pH. A measure that reflects in vivo conditions better is the conditional stability constant, which reflects chelate stability at physiologic pH (pH 7.4); these values are shown in Table 1 for several Gd-based CM.

Differences in thermodynamic stability constants between gadolinium chelates do not appear to explain the reported numbers of cases of NSF. Subject to the caveats described above with regard to the unreliability of spontaneous adverse event reporting, it is clear that stability measures alone do not explain the reporting to date. The stability measure by itself implies two broad groups of agents with very different stability levels, yet the numbers of cases reported for some agents are higher than reported for other agents with similar values. Further complications are evident when the conditional values are considered: Magnevist (gadopentetate) is suggested to be more stable than ProHance (gadoteridol) by this measure, which again is not consistent with the current totals of reported cases (though they are subject to change).

Table 1: Stability constants for several Gd-based CM

	Gadobenate	Gadoteridol	Gadopentetate	Gadoversetamide	Gadodiamide
Stability log K_{therm}	22.6	23.8	22.5	16.6	16.9
Conditional Stability	18.4	17.1	18.4	15	14.9

Clearly more needs to be considered in evaluating *in vivo* behavior of contrast agents. Cacheris et al (21) attempted to clarify the situation using "biospeciation" calculations, which take into account the relative stabilities of possible complexes. They defined the selectivity constant (K_{sel}), which is a hybrid constant applicable at pH 7.4 that takes into account the various possible ion exchange reactions in the body. K_{sel} indicates the selectivity of the ligand for gadolinium over endogenous ions (hydrogen, zinc, copper, calcium; iron was not included in their calculations because it is so tightly bound to ferritin as to be unavailable for reaction).

The selectivity constants of several Gd chelates indicate a good correlation with toxicity in animal studies (21). It should be noted that gadodiamide (GdDTPA-BMA), with a high K_{sel} value, also has a high LD50 value, i.e., low acute toxicity. Using K_{sel}, gadodiamide is also predicted to be 2 log units (100 times) more stable in relation to gadolinium exchange than gadopentetate, weakening the case that stability measures correlate with the numbers of reported NSF cases.

The LD50 of gadodiamide (GdDTPA-BMA) can be made even higher (less toxic) through the addition of extra ligand (caldiamide sodium [CaNaDTPA-BMA]). A 1% excess of caldiamide sodium increases the LD50 of Omniscan from 14 to 34 mmol/kg, and 5% excess (utilized in the commercial Omniscan formulation) optimises this effect, giving an LD50 of 38 mmol/kg (21). A possible mechanism of how the extra ligand reduces acute toxicity was proposed by these authors. The hypothesis states that the excess ligand reduces the potential toxicity of gadodiamide by reducing Gd-Zn transmetalation in vivo since endogenous zinc will displace Ca from CaNaDTPA-BMA and is therefore no longer available for displacing gadolinium from gadodiamide. It may also drive the chelation reaction more to completion. In the paper by Cacheris, the data also indicate that for several gadolinium chelates, despite a 50-fold difference in LD50 values based on administered dosage, all become lethally toxic to half the mice treated (i.e. the LD50), when they release 13-15 µM gadolinium. This can be taken as an indication of in vivo stability and, according to the data, GdDTPA-BMA has a very favourable profile.

Pharmacokinetic Studies

Several studies have investigated the pharmacokinetics of gadodiamide *in vivo*. These indicate that the kinetics of tissue uptake and release of GdDTPA-BMA are different than those of free gadolinium, and show that GdDTPA-BMA is stable in plasma and is excreted unchanged in the urine (22-24).

If Omniscan was prone to dechelation in vivo, then it would be expected that this would lead to detection of metabolites, and for the distribution and retention kinetics to resemble that of the free Gd metal. However, the study by Normann and Hals (24) showed that there is no detectable metabolism of the injected chelates, even in patients with prolonged retention due to renal impairment, and the distribution of gadodiamide is quantitatively and qualitatively different from that of the free Gd metal. For instance, the biotransformation of ^{14}C-gadodiamide was studied in rats after i.v. injection of 0.3 mmol/kg of a radiolabeled formulation of gadodiamide injection. Biotransformation in blood was negligible, and gadodiamide was excreted unchanged in the urine. These findings were supported by autoradiography data, which showed that the tissue distribution of ^{153}Gd-labelled gadodiamide was similar to that of ^{14}C-labelled gadodiamide, demonstrating that both metal and ligand behaved in exactly the same way (25). Supporting evidence comes from a study showing that the serum concentration of total gadolinium, analysed by inductive coupled plasma-atomic emission spectroscopy (ICP-AES), was identical to the serum concentration of the gadodiamide complex analysed by HPLC, indicating that all gadolinium was in the form of the gadodiamide complex (25).

The serum and peritoneal dialysate samples from end-stage renal disease patients were analysed for the concentrations of gadolinium and GdDTPA-BMA by ICP-AES and HPLC, respectively (26). Samples obtained 2, 4, and 7 days after dosing were compared with similar samples obtained shortly after dosing. There were no differences in the results using the two different methods of chemical analysis at the

1 hr, 2, 4, or 7 days post-dosing time-points. These data showed that there was no measurable transmetalation of GdDTPA-BMA during the 7-day post-treatment period, or degradation of the ligand. In addition, a separate study showed that urine from renally impaired patients treated with Omniscan also had no evidence of biotransformation (27).

Retention in Tissues

Two studies have suggested that more gadolinium was detectable in human bone following Omniscan administration (compared to ProHance®), interpreted as evidence of greater *in vivo* dechelation of Omniscan (28,29). However, the measured amounts of gadolinium were not adjusted for the different time intervals between administration of the contrast agents and analyses. In fact, the Omniscan group had a considerably shorter interval for elimination, which would bias the results against Omniscan. Furthermore, it should be noted that the analytical methods used in that study can only detect the gadolinium ion and cannot distinguish between the intact gadolinium complexes of the different contrast agents and uncomplexed "free" gadolinium. Finally, the relative amounts of retained gadolinium do not correlate with stability constants, or with the numbers of reported cases of NSF. Consequently, the results of such studies should be treated with caution.

Tweedle reported that more gadodiamide was retained in mice and rats compared to other contrast media (30). The relevance of these findings to humans is not clear. Moreover, a major concern with this article is that the measured amounts of gadolinium-153 were not corrected for the number of elimination half-lives that elapsed between administration and analysis. Another caveat is that the gadolinium chelates were prepared in the laboratory of the investigators and may not be reflective of the chemical composition or purity of the commercial formulations. The ratios of retained amounts do not correlate with stability constants, K_{sel} values, or the numbers of reported cases of NSF.

Boyd et al (31) reported finding traces of gadolinium in skin biopsy specimens from 4 patients with NSF. They did not report the actual amounts of gadolinium, and did not study control patients who received Gd-based CM without the development of NSF. Similarly, High et al (32) detected gadolinium in specimens from 4 of 7 patients with documented NSF who were exposed to gadolinium-based contrast. No gadolinium was detected in a paraffin-embedded specimen from a patient without NSF (it was not stated whether this patient had ever been exposed to gadolinium before). These pilot studies have methodological limitations, namely detection method, low number of specimens, and choice of controls. The finding of gadolinium by High et al in the tissues was not consistent and does not establish that these traces of Gd are only found in patients with NSF and not in other patients exposed to Gd-based contrast media. The relevance of the findings to the ætiology of NSF remains uncertain.

No human studies have provided compelling evidence of in vivo transmetalation or other type of gadolinium release after administration of Gd based contrast agents. Therefore, GEHC believes, there is insufficient evidence to support treating Omniscan differently from other gadolinium-based agents. On the contrary, the fact that NSF is associated with other Gd-containing agents makes a compelling case for regarding this as a possible class effect.

Summary of Stability Data

In vivo stability of the Gd chelates is important to limit the release of the toxic Gd metal. Several factors are believed to play roles in influencing the stability of Gd chelates:

- The intrinsic thermodynamic stability constant (K_{therm}), reflecting the affinity of a metal for a ligand is dependent on the conditions under which it is measured, and is greatly influenced by pH. Differences in thermodynamic stability constants between gadolinium chelates do not correlate with acute toxicity or reported numbers of cases of NSF.

- The selectivity constant (K_{sel}), the selectivity of the ligand for the bound metal over other endogenous ions, particularly zinc. Gadodiamide (GdDTPA-BMA) has a high K_{scl} value. K_{scl} correlates better with acute toxicity (LD50) than does K_{therm}, and though related to stability, does not correlate with numbers of NSF cases reported to date.
- Kinetics, the rate of the transmetalation reactions which, if substantially slower than their clearance rates, can result in significantly lower toxicity than predicted by the thermodynamic stability constant, solubility and selectivity. Studies of the recovery of gadodiamide from patients with renal failure do not provide evidence of dechelation or transmetalation, despite prolonged elimination.

The different measures of stability indicate that *in vitro* measurement in simple solutions is, of itself, insufficient to predict *in vivo* behaviour or toxicity. The *in vivo* stability of the Gd chelates may involve the interplay between a number of different variables including pH, other metal ions, endogenous ligands that can bind Gd and precipitating anions, as well as the elimination time in relation to the stability kinetics. All of these different factors may play a role in determining the stability of the Gd chelate, the release of Gd, and hence toxicity. Predictions of *in vivo* stability and toxicity of Gd chelates based on a single *in vitro* measure of stability such as thermodynamic stability are therefore inadequate.

If gadodiamide were prone to dechelation in vivo, then it would be expected that this would lead to detection of metabolites, and for the distribution and retention kinetics to resemble that of the free Gd metal. However, several studies have shown that there is no detectable metabolism of the injected chelates, even in patients with prolonged retention due to renal impairment, and the distribution of gadodiamide is quantitatively and qualitatively different to that of the free Gd metal.

Irrespective of these theoretical concerns over the stability of the different contrast agents and the possible role of Gd, the case reports of NSF from a number of countries show that several agents are associated with the development of NSF, indicating that, to the extent NSF is associated with the class of Gd-based contrast agents, it is a class-wide effect.

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GE Healthcare

ONC-2S-OSLO

OMNISCAN™ (gadodiamide) Injection

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all of the information needed to use OMNISCAN safely and effectively. See full prescribing information for OMNISCAN.

OMNISCAN™ (gadodiamide) injection for Intravenous Use

Initial U.S. Approval: 1993

WARNING: NOT FOR INTRATHECAL USE and NEPHROGENIC SYSTEMIC FIBROSIS (NSF)

See full prescribing information for complete boxed warning.

NOT FOR INTRATHECAL USE

- **Inadvertent intrathecal use of OMNISCAN has caused convulsions, coma, sensory and motor neurologic deficits (5.4).**

NSF

- **Gadolinium-based contrast agents (GBCAs) increase risk of NSF in patients with:**
  - **acute or chronic severe renal insufficiency (glomerular filtration rate < 30 mL/min/1.73m²), or**
  - **acute renal insufficiency of any severity due to hepato-renal syndrome or in perioperative liver transplantation period.**
- **In these patients, avoid use of GBCAs unless diagnostic information is essential and not available with non-contrast enhanced MRI.**

NSF may result in fatal or debilitating systemic fibrosis affecting the skin, muscle, and internal organs (5.2).

RECENT MAJOR CHANGES

• Boxed Warning: Nephrogenic Systemic Fibrosis (NSF)	9/2007
• Warnings and Precautions: hypersensitivity reactions, NSF, acute renal failure, inadvertent intrathecal use (5.1, 5.2, 5.3, 5.4)	9/2007

INDICATIONS AND USAGE

OMNISCAN is a gadolinium-based contrast agent for diagnostic magnetic resonance imaging (MRI) indicated for intravenous use to:

- Visualize lesions with abnormal vascularity in the brain, spine, and associated tissues (1.1)
- Facilitate the visualization of lesions with abnormal vascularity within the thoracic, abdominal, pelvic cavities, and the retroperitoneal space (1.2)

DOSAGE AND ADMINISTRATION

- CNS – Adults and Pediatrics; 2-16 years of age: 0.2 mL/kg (0.1 mmol/kg) (2.1, 2.4)
- Body – Adults and Pediatrics; 2-16 years of age:
  Kidney: 0.1 mL/kg (0.05 mmol/kg)
  Intrathoracic, intra-abdominal, and pelvic cavities: 0.2 mL/kg (0.1 mmol/kg) (2.2, 2.4)

DOSAGE FORMS AND STRENGTHS

Sterile aqueous solution for intravenous injection; 287 mg/mL (3)

CONTRAINDICATIONS

None

WARNINGS AND PRECAUTIONS

- *Anaphylactoid and other serious hypersensitivity reactions* including fatal reactions have occurred particularly in patients with history of allergy or drug reactions. Monitor patients closely for need of emergency cardiorespiratory support (5.1).
- *Nephrogenic Systemic Fibrosis (NSF)* has occurred in patients with severe renal insufficiency. Higher than recommended dosing or repeat dosing appears to increase the risk (5.2).
- *Acute renal failure* has occurred in patients with preexisting renal insufficiency. Use the lowest necessary dose of OMNISCAN and evaluate renal function in these patients (5.3).

ADVERSE REACTIONS

- The most frequent adverse reactions (≤ 3%) observed during OMNISCAN adult clinical studies were nausea, headache, and dizziness (6.1)
- Serious or life-threatening reactions include: cardiac failure, arrhythmia and myocardial infarction (6.1, 6.3)

To report SUSPECTED ADVERSE REACTIONS, contact GE Healthcare at 1-800-654-0118 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 9/2007

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: NOT FOR INTRATHECAL USE and NEPHROGENIC SYSTEMIC FIBROSIS (NSF)

NOT FOR INTRATHECAL USE

Inadvertent intrathecal use of OMNISCAN has caused convulsions, coma, sensory and motor neurologic deficits (5.4).

NSF

Gadolinium-based contrast agents increase the risk for NSF in patients with:

- **acute or chronic severe renal insufficiency (glomerular filtration rate < 30 mL/min/1.73m²), or**
- **acute renal insufficiency of any severity due to the hepato-renal syndrome or in the perioperative liver transplantation period.**

In these patients, avoid use of gadolinium-based contrast agents unless the diagnostic information is essential and not available with non-contrast enhanced magnetic resonance imaging (MRI). NSF may result in fatal or debilitating systemic fibrosis affecting the skin, muscle, and internal organs. Screen all patients for renal dysfunction by obtaining a history and laboratory tests. When administering a gadolinium-based contrast agent, do not exceed the recommended dose and allow a sufficient period of time for elimination of the agent from the body prior to any readministration (*see Warnings and Precautions (5.2)*).

1 INDICATIONS AND USAGE

1.1 CNS (Central Nervous System)

OMNISCAN is a gadolinium-based contrast agent indicated for intravenous use in MRI to visualize lesions with abnormal vascularity (or those thought to cause abnormalities in the blood-brain barrier) in the brain (intracranial lesions), spine, and associated tissues *[see Clinical Studies (14.1)]*.

1.2 Body (Intrathoracic (noncardiac), Intra-abdominal, Pelvic and Retroperitoneal Regions)

OMNISCAN is a gadolinium-based contrast agent indicated for intravenous use to facilitate the visualization of lesions with abnormal vascularity within the thoracic (noncardiac), abdominal, pelvic cavities, and the retroperitoneal space *[see Clinical Studies (14.2)]*.

2 DOSAGE AND ADMINISTRATION

2.1 CNS (Central Nervous System)

Adults: The recommended dose of OMNISCAN is 0.2 mL/kg (0.1 mmol/kg) administered as a bolus intravenous injection. An additional 0.4 mL/kg (0.2 mmol/kg) can be given within 20 minutes of the first dose. *[see Dosage Chart, Dosage and Administration (2.43)]*.

Pediatric Patients (2-16 years): The recommended dose of OMNISCAN is 0.2 mL/kg (0.1 mmol/kg) administered as a bolus intravenous injection. *[see Dosage Chart, Dosage and Administration (2.43)]*.

2.2 Body (Intrathoracic (noncardiac), Intra-abdominal, Pelvic and Retroperitoneal Regions)

Adult and Pediatric Patients (2-16 years of age): For imaging the kidney, the recommended dose of OMNISCAN is 0.1 mL/kg (0.05 mmol/kg). For imaging the intrathoracic (noncardiac), intra-abdominal, and pelvic cavities, the recommended dose of OMNISCAN is 0.2 mL/kg (0.1 mmol/kg) *[see Dosage and Administration (2.3)]*.

2.3 Dosage Chart

BODY WEIGHT		PEDIATRIC (mmol/kg)		ADULTS (mmol/kg)		
		0.05	0.1	0.05	0.1	0.2
kg	lb	VOLUME (mL)		VOLUME (mL)		
12	26	1.2	2.4	-	-	-
14	31	1.4	2.8	-	-	-
16	35	1.6	3.2	-	-	-
18	40	1.8	3.6	-	-	-
20	44	2	4	-	-	-
22	48	2.2	4.4	-	-	-
24	53	2.4	4.8	-	-	-
26	57	2.6	5.2	-	-	-
28	62	2.8	5.6	-	-	-
30	66	3	6	-	-	-
40	88	4	8	4	8	16
50	110	5	10	5	10	20
60	132	6	12	6	12	24
70	154	7	14	7	14	28
80	176	8	16	8	16	32
90	198	-	-	9	18	36
100	220	-	-	10	20	40
110	242	-	-	11	22	44
120	264	-	-	12	24	48
130*	286	-	-	13	26	52

*The heaviest patient in clinical studies weighed 136 kg.

2.4 Dosing Guidelines

Inspect OMNISCAN visually for particulate matter and discoloration before administration, whenever solution and container permit.

Do not use the solution if it is discolored or particulate matter is present.

Draw OMNISCAN into the syringe and use immediately. Discard any unused portion of OMNISCAN Injection.

To ensure complete delivery of the desired volume of contrast medium, follow the injection of OMNISCAN with a 5 mL flush of 0.9% sodium chloride, as provided in the Prefill Plus needle-free system. Complete the imaging procedure within 1 hour of administration of OMNISCAN.

2.5 Repeat Dosing

Sequential use during the same diagnostic session has been studied in adult CNS use only. If the physician determines repeat dosing is required in non-CNS imaging in adults or pediatric patients, renal function should be normal and the time interval between repeat doses should be at least 7 hours to allow for clearance of the drug from the body *[see Clinical Pharmacology (12.3)]*.

3 DOSAGE FORMS AND STRENGTHS

Sterile aqueous solution for intravenous injection; 287 mg/mL.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions

Anaphylactoid and anaphylactic reactions, with cardiovascular, respiratory and cutaneous manifestations, resulting in death have occurred. If such a reaction occurs, stop OMNISCAN Injection and immediately begin appropriate therapy. Observe patients closely, particularly those with a history of drug reactions, asthma, allergy or other hypersensitivity disorders, during and up to several hours after OMNISCAN Injection.

5.2 Nephrogenic Systemic Fibrosis [see Boxed Warning]

Gadolinium-based contrast agents increase the risk for nephrogenic systemic fibrosis (NSF) in patients with acute or chronic severe renal insufficiency (glomerular filtration rate < 30 mL/min/1.73m²) and in patients with acute renal insufficiency of any severity due to the hepato-renal syndrome or in the perioperative liver transplantation period. In these patients, avoid use of gadolinium-based contrast agents unless the diagnostic information is essential and not available with non-contrast enhanced MRI. For patients receiving hemodialysis, physicians may consider the prompt initiation of hemodialysis following the administration of a gadolinium-based contrast agent in order to enhance the contrast agent's elimination. The usefulness of hemodialysis in the prevention of NSF is unknown.

Among the factors that may increase the risk for NSF are repeated or higher than recommended doses of a gadolinium-based contrast agent and the degree of renal function impairment at the time of exposure.

Postmarketing reports have identified the development of NSF following single and multiple administrations of gadolinium-based contrast agents. These reports have not always identified a specific agent. Where a specific agent was identified, the most commonly reported agent was gadodiamide (Omniscan™), followed by gadopentetate dimeglumine (Magnevist®) and gadoversetamide (OptiMARK®). NSF has also developed following the sequential administrations of gadodiamide with gadobenate dimeglumine (MultiHance®) or gadoteridol (ProHance®). The number of postmarketing reports is subject to change over time and may not reflect the true proportion of cases associated with any specific gadolinium-based contrast agent.

The extent of risk for NSF following exposure to any specific gadolinium-based contrast agent is unknown and may vary among the agents. Published reports are limited and predominantly estimate NSF risks with gadodiamide. In one retrospective study of 370 patients with severe renal insufficiency who received gadodiamide, the estimated risk for development of NSF was 4% (J Am Soc Nephrol 2006;17:2359). The risk, if any, for the development of NSF among patients with mild to moderate renal insufficiency or normal renal function is unknown.

Screen all patients for renal dysfunction by obtaining a history and/or laboratory tests. When administering a gadolinium-based contrast agent, do not exceed the recommended dose and allow a sufficient period of time for elimination of the agent prior to any readministration (see *Clinical Pharmacology (12.2) and Dosage and Administration (2)*).

5.3 Acute Renal Failure

In patients with renal insufficiency, acute renal failure requiring dialysis or worsening renal function have occurred, mostly within 48 hours of OMNISCAN Injection. The risk of renal failure may increase with increasing dose of gadolinium contrast. Use the lowest necessary dose of contrast and evaluate renal function in patients with renal insufficiency. Acute renal failure was observed in < 1% of patients in OMNISCAN clinical studies *[see Adverse Reactions (6)]*.

OMNISCAN is cleared by glomerular filtration. Hemodialysis also enhances OMNISCAN clearance *[see Use in Specific Populations (8.5, 8.6)]*.

5.4 Not for Intrathecal Use

Inadvertent intrathecal use of OMNISCAN has occurred and caused convulsions, coma, sensory and motor neurologic deficits.

5.5 Impaired Visualization of Lesions Detectable with Non-contrast MRI

Paramagnetic contrast agents such as OMNISCAN might impair the visualization of lesions which are seen on the non-contrast MRI. This may be due to effects of the paramagnetic contrast agent, or imaging parameters. Exercise caution when OMNISCAN MRI scans are interpreted in the absence of a companion non-contrast MRI.

5.6 Laboratory Test Findings

Asymptomatic, transitory changes in serum iron have been observed. The clinical significance is unknown.

OMNISCAN interferes with serum calcium measurements with some colorimetric (complexometric) methods commonly used in hospitals, resulting in serum calcium concentrations lower than the true values. In patients with normal renal function, this effect lasts for 12-24 hours. In patients with decreased renal function, the interference with calcium measurements is

expected to last during the prolonged elimination of OMNISCAN. After patients receive OMNISCAN, careful attention should be used in selecting the type of method used to measure calcium.

6 ADVERSE REACTIONS

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

6.1 Clinical Studies Experience (Adults)

In clinical studies 1160 patients were exposed to OMNISCAN. The most frequent adverse reactions were nausea, headache, and dizziness that occurred in 3% or less of the patients.

The following adverse reactions occurred in 1% or less of patients:

Application Site Disorders: Injection site reaction.

Autonomic Nervous System Disorders: Vasodilation.

Body as a Whole-General Disorders: Anaphylactoid reactions (characterized by cardiovascular, respiratory, and cutaneous symptoms), fever, hot flushes, rigors, fatigue, malaise, pain, syncope.

Cardiovascular Disorders: Cardiac failure, rare arrhythmia and myocardial infarction resulting in death in patients with ischemic heart disease, flushing, chest pain, deep thrombophlebitis.

Central and Peripheral Nervous System Disorders: Convulsions including grand mal, ataxia, abnormal coordination, paresthesia, tremor, aggravated multiple sclerosis (characterized by sensory and motor disturbances), aggravated migraine.

Gastrointestinal System Disorders: Abdominal pain, diarrhea, eructation, dry mouth/vomiting, melena.

Hearing and Vestibular Disorders: Tinnitus.

Liver and Biliary System Disorders: Abnormal hepatic function.

Musculoskeletal System Disorders: Arthralgia, myalgia.

Respiratory System Disorders: Rhinitis, dyspnea.

Skin and Appendage Disorders: Pruritus, rash, erythematous rash, sweating increased, urticaria.

Special Senses, Other Disorders: Taste loss, taste perversion.

Urinary System Disorders: Acute reversible renal failure.

Vision Disorders: Abnormal vision.

6.2 Clinical Studies Experience (Pediatrics)

In the 97 pediatric patients in CNS studies with OMNISCAN [*see Clinical Studies (14.1)*] and the 144 pediatric patients in published literature, the adverse reactions were similar to those reported in adults.

6.3 Postmarketing Experience

Because postmarketing reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

The following adverse reactions have been identified during the postmarketing use of OMNISCAN:

Nervous System Disorders: Inadvertent intrathecal use causes seizures, coma, paresthesia, paresis.

General Disorders: Nephrogenic Systemic Fibrosis (NSF) [*see Warnings and Precautions (5.2)*].

7 DRUG INTERACTIONS

Specific drug interaction studies have not been conducted.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C: OMNISCAN has been shown to have an adverse effect on embryo-fetal development in rabbits at dosages as low as 0.5 mmol/kg/day for 13 days during gestation (approximately 0.6 times the human dose based on a body surface area comparison). These adverse effects are observed as an increased incidence of flexed appendages and skeletal malformations which may be due to maternal toxicity since the body weight of the dams was reduced in response to OMNISCAN administration during pregnancy. In rat studies, fetal abnormalities were not observed at doses up to 2.5 mmol/kg/day for 10 days during gestation (1.3 times the maximum human dose based on a body surface area comparison); however, maternal toxicity was not achieved in these studies and a definitive conclusion about teratogenicity in rats at doses above 2.5 mmol/kg/day cannot be made. Adequate and well controlled studies in pregnant women have not been conducted. OMNISCAN should only be used during pregnancy if the potential benefit justifies the potential risk to the fetus.

8.3 Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, exercise caution when administering OMNISCAN to a nursing woman.

8.4 Pediatric Use

The safety and efficacy of OMNISCAN at a single dose of 0.05 to 0.1 mmol/kg have been established in pediatric patients over 2 years of age based on adequate and well controlled studies of OMNISCAN in adults, a pediatric CNS imaging study, and safety data in the scientific literature. However, the safety and efficacy of doses greater than 0.1 mmol/kg and of repeated doses have not been studied in pediatric patients.

Pharmacokinetics of OMNISCAN have not been studied in pediatrics. The glomerular filtration rate of neonates and infants is much lower than that of adults. The pharmacokinetics volume of distribution is also different. Therefore, the optimal dosing regimen and imaging times in patients under 2 years of age have not been established.

8.5 Geriatric Use

In clinical studies of OMNISCAN, 243 patients were between 65 and 80 years of age while 15 were over 80. No overall differences in safety or effectiveness were observed between these patients and younger patients. Other reported clinical experience has not identified differences in response between the elderly and younger patients, but greater sensitivity in the elderly cannot be ruled out. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

OMNISCAN is excreted by the kidney, and the risk of toxic reactions to OMNISCAN may be greater in patients with impaired renal function [*see Warnings and Precautions (5.3)*]. Because elderly patients are more likely to have decreased renal function, select dose carefully and consider assessment of renal function before OMNISCAN use.

8.6 Renal/Hepatic Impairment

Dose adjustments in renal or hepatic impairment have not been studied. Caution should be exercised in patients with impaired renal insufficiency [*see Warnings and Precautions (5.2, 5.3)*].

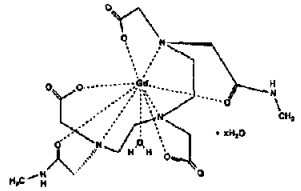
10 OVERDOSAGE

Clinical consequences of overdose with OMNISCAN have not been reported. The minimum lethal dose of intravenously administered OMNISCAN in rats and mice is greater than 20 mmol/kg (200 times the recommended human dose of 0.1 mmol/kg; 67 times the cumulative 0.3 mmol/kg dose). OMNISCAN is dialyzable.

11 DESCRIPTION

OMNISCAN (gadodiamide) Injection is the formulation of the gadolinium complex of diethylenetriamine pentaacetic acid bismethylamide, and is an injectable, nonionic extracellular enhancing agent for magnetic resonance imaging. OMNISCAN is administered by intravenous injection.

OMNISCAN is provided as a sterile, clear, colorless to slightly yellow, aqueous solution. Each 1 mL contains 287 mg gadodiamide and 12 mg caldiamide sodium in Water for Injection. The pH is adjusted between 5.5 and 7.0 with hydrochloric acid and/or sodium hydroxide. OMNISCAN contains no antimicrobial preservative. OMNISCAN is a 0.5 mol/L solution of aqua[5,8-bis(carboxymethyl)-11-[2-(methylamino)-2-oxoethyl]-3-oxo-2,5,8,11-tetraazatridecan-13-oato (3-)-N^5, N^8, N^{11}, O^3, O^5, O^8, O^{11}, O^{13}] gadolinium hydrate, with a molecular weight of 573.66 (anhydrous), an empirical formula of $C_{16}H_{28}GdN_5O_8 \cdot xH_2O$, and the following structural formula:



Pertinent physicochemical data for OMNISCAN are noted below:

PARAMETER		
Osmolality (mOsmol/kg water)	@ 37°C	789
Viscosity (cP)	@ 20°C	2
	@ 37°C	1.4
Density (g/mL)	@ 25°C	1.14
Specific gravity	@ 25°C	1.15

OMNISCAN has an osmolality approximately 2.8 times that of plasma at 37°C and is hypertonic under conditions of use.

12 CLINICAL PHARMACOLOGY

12.1 Pharmacodynamics

In magnetic resonance imaging, visualization of normal and pathologic tissue depends in part on variations in the radiofrequency signal intensity. These variations occur due to: changes in proton density; alteration of the spin-lattice or longitudinal relaxation time (T_1); and variation of the spin-spin or transverse relaxation time (T_2). OMNISCAN is a paramagnetic agent with unpaired electron spins which generate a local magnetic field. As water protons move through this local magnetic field, the changes in magnetic field experienced by the protons reorient them with the main magnetic field more quickly than in the absence of a paramagnetic agent.

By increasing the relaxation rate, OMNISCAN decreases both the T_1 and T_2 relaxation times in tissues where it is distributed. At clinical doses, the effect is primarily on the T_1 relaxation time, and produces an increase in signal intensity. OMNISCAN does not cross the intact blood-brain barrier and, therefore, does not accumulate in normal brain or in lesions that do not have an abnormal blood-brain barrier (e.g., cysts, mature postoperative scars). However, disruption of the blood-brain barrier or abnormal vascularity allows accumulation of OMNISCAN in lesions such as neoplasms, abscesses, and subacute infarcts. The pharmacokinetic parameters of OMNISCAN in various lesions are not known. There is no detectable biotransformation or decomposition of gadodiamide.

Pharmacokinetic and pharmacodynamic studies have not been systematically conducted to determine the optimal dose and optimal imaging time in patients with abnormal renal function or renal failure, in the elderly, or in pediatric patients with immature renal function.

12.3 Pharmacokinetics

The pharmacokinetics of intravenously administered gadodiamide in normal subjects conforms to an open, two-compartment model with mean distribution and elimination half-lives (reported as mean ± SD) of 3.7 ± 2.7 minutes and 77.8 ± 16 minutes, respectively.

Gadodiamide is eliminated primarily in the urine with 95.4 ± 5.5% (mean ± SD) of the administered dose eliminated by 24 hours. The renal and plasma clearance rates of gadodiamide are nearly identical (1.7 and 1.8 mL/min/kg, respectively), and are similar to that of substances excreted primarily by glomerular filtration. The volume of distribution of gadodiamide (200 ± 61 mL/kg) is equivalent to that of extracellular water. Gadodiamide does not bind to human serum proteins *in vitro*. Pharmacokinetic and pharmacodynamic studies have not been systematically conducted to determine the optimal dose and imaging time in patients with abnormal renal function or renal failure, in the elderly, or in pediatric patients with immature renal function.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long term animal studies have not been performed to evaluate the carcinogenic potential of gadodiamide. The results of the following genotoxicity assays were negative: *in vitro* bacterial reverse mutation assay, *in vitro* Chinese Hamster Ovary (CHO)/Hypoxanthine Guanine Phosphoribosyl Transferase (HGPT) forward mutation assay, *in vitro* CHO chromosome aberration assay, and the *in vivo* mouse micronucleus assay at intravenous doses of 27 mmol/kg (approximately 7 times the maximum human dose based on a body surface area comparison). Impairment of male or female fertility was not observed in rats after intravenous administration three times per week at the maximum dose tested of 1.0 mmol/kg (approximately 0.5 times the maximum human dose based on a body surface area comparison).

14 CLINICAL STUDIES

14.1 CNS (Central Nervous System)

OMNISCAN (0.1 mmol/kg) contrast enhancement in CNS MRI was evident in a study of 439 adults. In a study of sequential dosing, 57 adults received OMNISCAN 0.1 mmol/kg followed by 0.2 mmol/kg within 20 minutes (for cumulative dose of 0.3 mmol/kg). The MRIs were compared blindly. In 54/56 (96%) patients, OMNISCAN contrast enhancement was evident with both the 0.1 mmol/kg and cumulative 0.3 mmol/kg OMNISCAN doses relative to non-contrast MRI.

In comparison to the non-contrast MRI, increased numbers of brain and spine lesions were noted in 42% of patients who received OMNISCAN at any dose. In comparisons of 0.1 mmol/kg versus 0.3 mmol/kg, the results were comparable in 25/56 (45%); in 1/56 (2%) OMNISCAN 0.1 mmol/kg dose provided more diagnostic value and in 30/56 (54%) the cumulative OMNISCAN 0.3 mmol/kg dose provided more diagnostic value.

The usefulness of a single 0.3 mmol/kg bolus in comparison to the cumulative 0.3 mmol/kg (0.1 mmol/kg followed by 0.2 mmol/kg) has not been established.

OMNISCAN as a single 0.1 mmol/kg dose was evaluated in 97 pediatric patients with a mean age of 8.9 (2-18) years referred for CNS MRI. Postcontrast MRI provided added diagnostic information, diagnostic confidence, and new patient management information in 76%, 67%, and 52%, respectively, of pediatrics.

14.2 Body (Intrathoracic (noncardiac), Intra-abdominal, Pelvic and Retroperitoneal Regions)

OMNISCAN was evaluated in a controlled trial of 276 patients referred for body MRI. These patients had a mean age of 57 (9-88) years. Patients received 0.1 mmol/kg OMNISCAN for imaging the thorax (noncardiac), abdomen, and pelvic organs, or a dose of 0.05 mmol/kg for imaging the kidney. Pre- and post-OMNISCAN images were evaluated blindly for the degree of diagnostic value rated on a scale of "remarkably improved, improved, no change, worse, and cannot be determined." The postcontrast results showed "remarkably improved" or "improved" diagnostic value in 90% of the thorax, liver, and pelvis patients, and in 95% of the kidney patients.

In a dose ranging study 258 patients referred for body MRI received OMNISCAN 0.025, 0.05, 0.1 mmol/kg. The lowest effective dose of OMNISCAN for the kidney was 0.05 mmol/kg.

16 HOW SUPPLIED/STORAGE AND HANDLING

OMNISCAN (gadodiamide) Injection is a sterile, clear, colorless to slightly yellow, aqueous solution containing 287 mg/mL of gadodiamide in in rubber stoppered vials and polypropylene syringes. OMNISCAN is supplied in the following sizes:

5 mL fill in 10 mL vial, box of 10 (NDC 0407-0690-05)

10 mL vial, box of 10 (NDC 0407-0690-10)

15 mL fill in 20 mL vial, box of 10 (NDC 0407-0690-15)

20 mL vial, box of 10 (NDC 0407-0690-20)

50 mL vial, box of 10 (NDC 0407-0690-55)

10 mL fill in 20 mL prefilled syringe, box of 10 (NDC 0407-0690-12)

15 mL fill in 20 mL prefilled syringe, box of 10 (NDC 0407-0690-17)

20 mL prefilled syringe, box of 10 (NDC 0407-0690-22)

Prefill Plus™ needle-free system

OMNISCAN 15 mL, box of 10 (NDC 0407-0691-62)

Contains: OMNISCAN 15 mL fill in 20 mL Single Dose Prefilled Syringe and 5 mL 0.9% Sodium Chloride Injection, USP I.V. Flush Syringe

Prefill Plus™ needle-free system

OMNISCAN 20 mL, box of 10 (NDC 0407-0691-63)

Contains: OMNISCAN 20 mL fill in 20 mL Single Dose Prefilled Syringe and 5 mL 0.9% Sodium Chloride Injection, USP I.V. Flush Syringe

Protect OMNISCAN from strong daylight and direct exposure to sunlight. **Do not freeze.** Freezing can cause small cracks in the vials, which would compromise the sterility of the product. Do not use if the product is inadvertently frozen.

Store OMNISCAN at controlled room temperature 20°-25°C (68°-77°F); excursions permitted to 15°-30°C (59°-86°F) (see USP).

17 PATIENT COUNSELING INFORMATION

Patients receiving OMNISCAN should be instructed to inform their physician if they:

- are pregnant or breast feeding, or
- have a history of renal disease, convulsions, asthma or allergic respiratory disorders, or recent administration of gadolinium-based contrast.

Gadolinium-based contrast agents increase the risk for NSF among patients with acute or chronic severe renal insufficiency or acute renal insufficiency due to the hepato-renal syndrome. This risk may increase with repetitive or higher than recommended doses of a gadolinium-based contrast agent. Instruct patients at increased risk for NSF to contact their physician if they develop burning, itching, swelling, scaling, hardening and tightening of the skin; red or dark patches on the skin; stiffness in joints with trouble moving, bending or straightening the arms, hands, legs or feet; pain deep in the hip bones or ribs; or muscle weakness.

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